UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,894	07/07/2003	James M. Hagberg	108172-00097	7034

4372 7590 02/27/2006

ARENT FOX PLLC
1050 CONNECTICUT AVENUE, N.W.
SUITE 400
WASHINGTON, DC 20036

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,894	HAGBERG ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/1/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The claims have been renumbered, pursuant to 37 CFR 1.126. In the orginial claims, the seventh claim is erroneously numbered '4.', with subsequent claims being numbered sequentially thereafter. The claim numbers referred to in this office action are in correspondence with the claims as renumbered.

Claims 1-18 are pending and examined on the merits.

Specification

1. The disclosure is objected to because of the following informalities: The title of Table 2 is not in agreement with the description of this table as provided in the specification (paragraph [0049]). The title of the table indicates that the data refers to fibrinolytic measures among different t-PA genotypes, whereas the description in the specification indicates that the data refer to subjects with different PAI-1 promoter genotypes.

Appropriate correction is required.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Väisänen et al (1999) as cited in the IDS.

Väisänen et al teaches methods comprising the steps of determining the genotype of a subject with respect to the 4G/5G PAI-1 gene promoter polymorphism (p.1118, left col., DNA analysis), and engaging the subject in an exercise program (p.1118, left col., Cardiorespiratory fitness and exercise intervention). The methods of Väisänen et al utilize the identification of subjects with 4G/4G, 4G/5G, and 5G/5G genotypes (Table 1), thus identifying subjects with at least one 4G allele as required by claims 1, 7, and 13.

Regarding claim 1, Väisänen et al teaches that PAI-1 is an inhibitor of fibrinolysis (p.1117, left col., Introduction), and that subjects were engaged in exercise that reduced PAI-1 activity (Table 1; p.1118, right col., lns.21-23), thus decreasing inhibition of fibrinolysis and increasing fibrinolysis.

Regarding claim 7, Väisänen et al teaches that elevated PAI-1 activity increases the risk of cardiovascular disease (p.1117, left col., Introduction). Thus the decrease in PAI-1 activity in the subjects would lead to a prevention in cardiovascular disease. Additionally, the reference teaches that exercise results in a decrease in plasma

triglycerides (p.1118, right col., lns.28-30), which would also decrease the likelihood of developing cardiovascular disease.

Regarding claim 13, Väisänen et al teaches subjects that, upon participation in exercise showed reduced PAI-1 activity (Table 1; p.1118, right col., lns.21-23), thus increased fibrinolysis. Such an increase in fibrinolytic activity would lead to an amelioration of cardiovascular disease by the removal of fibrin clots from the sites of vascular injury, which is the purpose of the fibrinolytic system.

Regarding claims 2, 3, 8, 9, 14, and 15, Väisänen et al teaches the analysis of subjects that were heterozygous (4G/5G) and homozygous for the 4G allele (4G/4G) at the promoter polymorphic site (p.1118, right col., lns.10-35), and that subjects from both of these groups responded to the exercise intervention (Table 1).

Regarding claims 4-6, 10-12, and 16-18, Väisänen et al teaches the particular nature of the exercise training with regards to duration of the regimen (p.1117, right col., Study design) and courses of exercise (p.1118, left col., Cardiorespiratory fitness and exercise intervention). The reference teaches that the study took place over three years, with exercise occurring three times a week for the first three months, followed by five times a week there after. This meets the definition of extensive exercise as defined in the specification (paragraph [0019]) as the exercise regimen of Väisänen et al includes at least 25 single courses of exercise, and takes place over about 400 days. Relevant to claims 6, 7, 11, 12, 17 and 18, because of the progressive nature of the definitions of limited and moderate exercise as defined in the instant specification

(paragraphs [0020]-[0021]), the exercise of Väisänen et al would inherently be comprised of both limited and moderate exercise.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide a method to increase fibrinolysis, prevent cardiovascular disease, or ameliorate cardiovascular disease in a subject, for which the PAI-1 gene promoter genotype has been determined, using exercise.

Nature of the Invention and Breadth of the Claims

The specification asserts that the instant invention relates to identifying genetic markers that correlate with improved success in increasing fibrinolysis levels in subjects through exercise training (paragraph [0003]). The claims are drawn to methods for effecting change in subjects with particular genotypes at the PAI-1 gene promoter polymorphic site using exercise training. Claims 1-6 are drawn to methods for increasing fibrinolysis in a subject. Claims 7-12 are drawn to methods for preventing

cardiovascular disease in a subject. Claims 13-18 are drawn to methods for ameliorating cardiovascular disease in a subject.

The claims encompass subjects with at least one 4G allele (i.e. both homozygous 4G/4G subjects and heterozygous 4G/5G subjects) (claims 1, 4-7, 10-13, 16-18), subjects with heterozygous (i.e. 4G/5G) genotypes (claims 2, 8, and 14), and subjects with homozygous 4G/4G genotypes (claims 3, 9, and 15). The claims encompass exercise regimens comprised of extensive exercise (claims 4, 10, and 16), moderate exercise (claims 5, 11, and 17), and limited exercise (claims 6, 12, and 18).

The claims encompass any subject organism that contains the PAI-1 gene.

The nature of the invention requires knowledge of a correlation between the specific PAI-1 gene promoter genotype of a subject and the response (with regard to fibrinolysis levels) of that subject to exercise training.

Direction provided by the specification and working example

The specification teaches an example in which subjects were analyzed for several parameters indicative of fibrinolysis levels (i.e. PAI-1 and t-PA activities and t-PA antigen (paragraph [0031]) prior to participation in an exercise program to establish baseline values, and then after participation in an exercise program (paragraph [0045]).

The specification further teaches the genotyping of the PAI-1 gene promoter with respect to the 4G/5G polymorphic site (paragraph [0042]) by PCR amplification followed by restriction enzyme analysis of the resulting amplicon.

The instant specification provides an analysis of the changes in the measured parameters among the three possible (4G/4G; 4G/5G; 5G/5G) PAI-1 genotypes. The

data indicate the following results: the average PAI-1 activity decreased for the 4G/4G and 5G/5G groups, and increased for the 4G/5G group; the average t-PA activity increased for all groups; the average t-PA antigen decreased for all groups. While the specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The instant specification does not provide any data concerning any sort of control group, for example a reference group that did not participate in an exercise program.

The specification asserts that improving fibrinolysis prevented the development of cardiovascular disease or alleviated symptoms of cardiovascular disease (paragraph [0007]). There is no indication that either of these two qualities was actually measured in any of the analyzed subjects; Example 1 indicates that subjects were in fact excluded from the study if they had cardiovascular disease.

The specification presents results only from a population of human male and female subjects age 50-70.

The specification presents results only from participation in moderate exercise training (paragraph [0047], Table 1). The specification provides no results from subjects that participated in extensive exercise, or subjects that were involved only in limited exercise.

State of the art, level of skill in the art, and level of unpredictability

The level of skill in the art with regard to identification of PAI-1 gene promoter genotypes is high, however the prior art shows that the level of unpredictability in correlating any particular individual's genotype with fibrinolysis levels in response to exercise is high.

Väisänen et al teaches an analysis of fibrinolytic activity response to exercise among groups of subjects with different PAI-1 gene promoter genotypes. Although the Väisänen reference was applied to the art rejection earlier in this Office Action, the reference is cited in this enablement rejection to demonstrate the state of the art and its unpredictability; the specification of the instant application cannot be considered enabling for the methods of Väisänen because the instant application does not present the same data, gathered from the same population, as Väisänen. The Väisänen reference indicates that PAI-1 activity decreases (thus an indicator of increased fibrinolysis) in subjects from all subject groups regardless of PAI-1 genotype, as well as in reference groups (who do not participates in exercise) with both the 4G/4G and 4G/5G genotypes (Table 1). While the reference indicates that only the decrease in PAI-1 activity seen in the 4G/4G exercise group is significant ($p=0.025$; Table 1), the reference also indicates that the findings need to be replicated in other controlled randomized exercise studies (p.1119, right col., lns.52-53).

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis is illustrated by the instant specification. Table 1 (paragraph [0047]) indicates p-values from ANOVA analysis of several fibrinolysis related

parameters that range from 0.189 to 0.802. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of p=0.05 would not be considered strong enough for the basis of a conclusion.

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis is further exemplified by Tiyasangthong (2001). Tiyasangthong examine the hypothesis that exercise training effects fibrinolytic variables (p.103), and that the changes in PAI-1 activity with exercise training is related to PAI-1 polymorphisms (p.107). The reference indicates that there is no statistically significant correlation in changes in the measures of fibrinolytic parameters (PAI-1 and t-PA activity, and t-PA antigen) with regard to PAI-1 gene promoter genotype (p.95; p.96, Table 7).

Furthermore, claims drawn to methods for preventing cardiovascular disease may be considered as encompassing those methods which completely keep even the most minor forms of cardiovascular disease from occurring; wherein the pertinent method step is engaging a subject in exercise training. And while there may be an inverse relationship between physical activity and the risk of developing cardiovascular disease, the prior art of Sesso et al (2000) indicates that participation in physical exercise is not sufficient to provide a guaranteed prevention of any form or type of cardiovascular disease (Table 2; p.976, right col., lns.44-53).

Quantity of experimentation required

There would be a large amount of experimentation required to make and use the claimed invention. In order to establish that there is any statistically significant association between PAI-1 gene promoter genotype and response to exercise, one would have to conduct a large case-control randomized study to compare fibrinolytic activity among subjects with different PAI-1 genotypes upon exposure to exercise training. Such a study may or may not indicate that there is an exercise dependent increase in fibrinolytic activity, prevention of cardiovascular disease, or amelioration of cardiovascular disease, that is associated with PAI-1 genotype in any particular population.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention.

Requirement For Information Under 37 C.F.R. 1.105

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

The examiner has cited a PhD dissertation from the University of Maryland, College Park, authored by Onanog Tiyasangthong. The citation for this reference (from ProQuest) indicates that the Adviser for this dissertation is a co-inventor of the instant application. The information requested is the earliest date of public availability (i.e. when a member of the public could first obtain the information contained in the document) for the reference (cited in the PTO-892 Notice of References Cited included with this office action): The title page of this document indicates the year of publication as 2001.

The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

Conclusion

No claim is free of the prior art. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600